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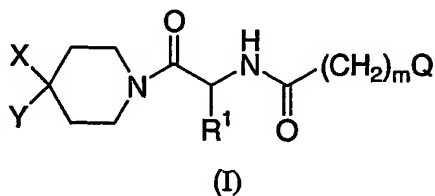
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(54) Title: SUBSTITUTED PIPERIDINES AS MELANOCORTIN RECEPTOR AGONISTS

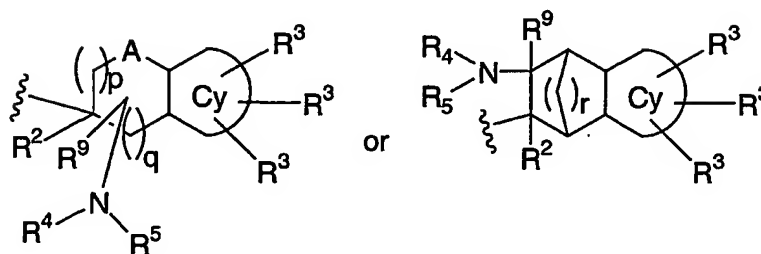
(57) Abstract: Certain novel 4-substituted piperidine compounds are agonists of the human melanocortin receptor(s) and, in particular, are selective agonists of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



- 5 wherein
Q is



Cy is selected from the group consisting of
aryl,

- 10 5- or 6-membered heteroaryl,
5- or 6-membered heterocyclyl, and
5- to 7-membered carbocyclyl;

wherein Cy is substituted with one to three groups independently selected from R³;

- 15 A is O, S(O)_m, NR⁷, or CH₂;

m is 0, 1, or 2;

n is 0, 1, 2, or 3;

p is 0, 1 or 2;

q is 0, 1 or 2;

- 20 r is 1, 2, or 3;

R¹ is selected from the group consisting of
hydrogen,

C₁₋₈ alkyl,
 (CHR⁷)_n-C₃₋₇ cycloalkyl,
 (CHR⁷)_naryl, and
 (CHR⁷)_nheteroaryl;

- 5 in which aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R⁶; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R⁶ and oxo;

R² is selected from the group consisting of

- 10 hydrogen,
 C₁₋₈ alkyl,
 (CH₂)_nC₃₋₇ cycloalkyl, and
 (CH₂)_n-aryl;

- 15 each R³ is independently selected from

- hydrogen,
 C₁₋₈ alkyl,
 (CH₂)_n-aryl,
 (CH₂)_nC₃₋₇ cycloalkyl,
 20 (CH₂)_n-heteroaryl,
 halo,
 OR⁷,
 NHSO₂R⁷,
 N(R⁷)₂,
 25 C≡N,
 CO₂R⁷,
 C(R⁷)(R⁷)N(R⁷)₂,
 NO₂,
 SO₂N(R⁷)₂,
 30 S(O)_mR⁷,
 CF₃, and
 OCF₃;

R⁴ and R⁵ are each independently selected from the group consisting of

hydrogen,
C₁₋₁₀ alkyl, and
C₃₋₈ cycloalkyl;

or R⁴ and R⁵ together with the nitrogen to which they are attached form a 5- to 8-
5 membered ring optionally containing an additional heteroatom selected from O, S,
and NR⁷;

wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups
independently selected from R⁶ and oxo;

10 R⁶ is selected from the group consisting of

C₁₋₈ alkyl,
(CH₂)_n-aryl,
(CH₂)_nC₃₋₇ cycloalkyl,
(CH₂)_n-heteroaryl,

15 halo,
OR⁷,
NHSO₂R⁷,
N(R⁷)₂,

20 C≡N,
CO₂R⁷,
C(R⁷)(R⁷)N(R⁷)₂,
NO₂,
SO₂N(R⁷)₂,
S(O)_mR⁷,
25 CF₃, and
OCF₃;

each R⁷ is independently selected from the group consisting of

30 hydrogen,
C₁₋₈ alkyl,
(CH₂)_n-aryl, and
(CH₂)_nC₃₋₇ cycloalkyl;

each R⁸ is independently selected from the group consisting of

35 hydrogen,

C₁₋₈ alkyl,
 (CH₂)_n-aryl,
 (CH₂)_n-heteroaryl, and
 (CH₂)_nC₃₋₇ cycloalkyl;

- 5 wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R⁶; and alkyl, cycloalkyl, and (CH₂)_n are unsubstituted or substituted with one to three groups independently selected from R⁶ and oxo; or two R⁸ groups together with the atoms to which they are attached form a 5- to 8-membered mono- or bi-cyclic ring system optionally containing an additional
 10 heteroatom selected from O, S, and NR⁷;

R⁹ is hydrogen or C₁₋₄ alkyl;

X is selected from the group consisting of

- 15 C₁₋₈ alkyl,
 (CH₂)_nC₃₋₈ cycloalkyl,
 (CH₂)_naryl,
 (CH₂)_nheteroaryl,
 (CH₂)_nheterocyclyl,
 20 (CH₂)_nC≡N,
 (CH₂)_nCON(R⁸R⁸),
 (CH₂)_nCO₂R⁸,
 (CH₂)_nCOR⁸
 (CH₂)_nNR⁸C(O)R⁸,
 25 (CH₂)_nNR⁸CO₂R⁸,
 (CH₂)_nNR⁸C(O)N(R⁸)₂,
 (CH₂)_nNR⁸SO₂R⁸,
 (CH₂)_nS(O)_mR⁸,
 (CH₂)_nSO₂N(R⁸)(R⁸),
 30 (CH₂)_nOR⁸,
 (CH₂)_nOC(O)R⁸,
 (CH₂)_nOC(O)OR⁸,
 (CH₂)_nOC(O)N(R⁸)₂,
 (CH₂)_nN(R⁸)(R⁸), and



wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R^6 , and alkyl, $(\text{CH}_2)_n$, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to four groups independently selected from R^6 and oxo;

5

Y is selected from the group consisting of

hydrogen,

C_{1-8} alkyl,

$(\text{CH}_2)_n\text{C}_{3-8}$ cycloalkyl,

10

$(\text{CH}_2)_n$ aryl,

$(\text{CH}_2)_n$ heterocyclyl, and

$(\text{CH}_2)_n$ heteroaryl;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R^6 ; and alkyl, $(\text{CH}_2)_n$, cycloalkyl, and heterocyclyl are optionally

15

substituted with one to three groups selected from R^6 and oxo;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein Cy is selected from the group consisting of benzene, pyridine, pyrazine, piperidine, and cyclohexane.

20

3. The compound of Claim 2 wherein Cy is benzene or cyclohexane.

25

4. The compound of Claim 1 wherein R^1 is $\text{CH}(\text{R}^7)$ -aryl or $\text{CH}(\text{R}^7)$ -heteroaryl wherein aryl and heteroaryl are optionally substituted with one or two R^6 groups.

5. The compound of Claim 4 wherein R^1 is benzyl optionally substituted with one or two groups selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 , and OCF_3 .

30

6. The compound of Claim 5 wherein R^1 is 4-chlorobenzyl, 4-fluorobenzyl, or 4-methoxybenzyl.

7. The compound of Claim 1 wherein R² is H or CH₃.

8. The compound of Claim 1 wherein X is (CH₂)_n-aryl,
5 (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC(O)N(R⁸)(R⁸), (CH₂)_nCO₂R⁸,
(CH₂)_nOR⁸, (CH₂)_nNR⁸C(O)R⁸, or (CH₂)_nNR⁸SO₂R⁸, wherein aryl and heteroaryl
are optionally substituted with one to three groups selected from R⁶; heterocyclyl is
optionally substituted with one to three groups selected from R⁶ and oxo; and the
(CH₂)_n group is optionally substituted with one to three groups selected from R⁷,
10 halo, S(O)_mR⁷, N(R⁷)₂, and OR⁷.

9. The compound of Claim 8 wherein X is CH₂-heteroaryl,
CH₂-heterocyclyl, NHC(O)R⁸, CO₂R⁸, or C(O)N(R⁸)(R⁸), wherein heteroaryl is
optionally substituted with one to three groups selected from R⁶; heterocyclyl is
15 optionally substituted with one to three groups selected from R⁶ and oxo; and wherein
R⁸ is each independently selected from H and C₁₋₆ alkyl optionally substituted with
OR⁷, SR⁷, or N(R⁷)₂, or 2 R⁷ groups together with the nitrogen to which they are
attached form a 5- or 6-membered ring optionally having an additional heteroatom
selected from O, S and NR⁷.

20

10. The compound of Claim 9 wherein heteroaryl is selected from
the group consisting of pyridyl, pyrazinyl, pyrimidinyl, triazolyl, tetrazolyl,
thiadiazolyl, oxadiazolyl, pyrazolyl, and imidazolyl.

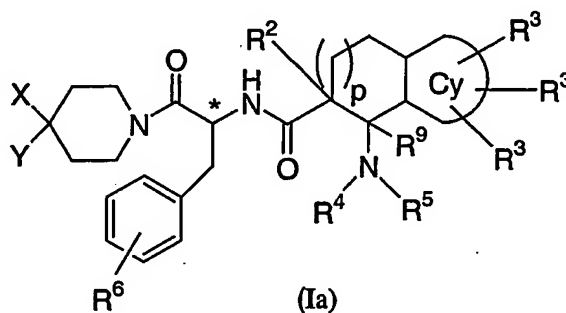
25 11. The compound of Claim 1 wherein Y is C₁₋₈ alkyl,
(CH₂)_nC₅₋₇ cycloalkyl, (CH₂)_n-aryl, (CH₂)_n-heterocyclyl or (CH₂)_n-heteroaryl,
wherein aryl and heteroaryl are optionally substituted with one to three groups
selected from R⁶; and (CH₂)_n, alkyl, cycloalkyl, and heterocyclyl are optionally
substituted with one to three groups selected from R⁶ and oxo.

30

12. The compound of Claim 11 wherein Y is cyclohexyl,
cycloheptyl, cyclopentyl, phenyl, or C₁₋₆ alkyl, unsubstituted or substituted with one
to three groups selected from R⁶ and oxo.

13. The compound of Claim 12 wherein Y is cyclohexyl or C₁₋₆ alkyl, wherein the cyclohexyl and alkyl groups are unsubstituted or substituted with one to three groups selected from R⁶ and oxo.

5 14. The compound of Claim 1 of formula Ia:



wherein

10 Cy is phenyl or cyclohexyl,
wherein Cy is substituted with one to three groups independently selected from R³;

n is 1 or 2;

p is 0, 1, or 2;

15

R² is selected from the group consisting of
hydrogen,
C₁₋₆ alkyl, and
C₅₋₆ cycloalkyl;

20

each R³ is independently selected from
hydrogen,
C₁₋₈ alkyl,
(CH₂)_n-aryl,
25 (CH₂)_nC₃₋₇ cycloalkyl,
(CH₂)_n-heteroaryl,
halo,

5 OR⁷,
 NH₂SO₂R⁷,
 N(R⁷)₂,
 C≡N,
 CO₂R⁷,
 C(R⁷)(R⁷)N(R⁷)₂,
 NO₂,
 SO₂N(R⁷)₂,
 S(O)_mR⁷,
 10 CF₃, and
 OCF₃;

R⁴ and R⁵ are each independently selected from the group consisting of
 hydrogen,
 15 C₁₋₆ alkyl, and
 C₅₋₆ cycloalkyl;

or R⁴ and R⁵ together with the nitrogen to which they are attached form a 5- to 8-
 membered ring optionally containing an additional heteroatom selected from O, S,
 and NR⁷;
 20 wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups
 independently selected from R⁶ and oxo;

R⁶ is selected from the group consisting of
 C₁₋₈ alkyl,
 25 (CH₂)_n-aryl,
 (CH₂)_nC₃₋₇cycloalkyl,
 (CH₂)_n-heteroaryl,
 halo,
 OR⁷,
 30 NH₂SO₂R⁷,
 N(R⁷)₂,
 C≡N,
 CO₂R⁷,
 C(R⁷)(R⁷)N(R⁷)₂,

NO₂,
SO₂N(R⁷)₂,
S(O)_mR⁷,
CF₃, and
5 OCF₃;

each R⁷ is independently selected from the group consisting of
hydrogen,
C₁₋₈ alkyl, and
10 C₃₋₆ cycloalkyl;

each R⁸ is independently selected from the group consisting of
hydrogen,
C₁₋₅ alkyl,
15 aryl,
heteroaryl, and
C₅₋₆ cycloalkyl;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups
independently selected from R⁶; and alkyl and cycloalkyl are unsubstituted or
20 substituted with one to three groups independently selected from R⁶ and oxo; or two
R⁸ groups together with the atoms to which they are attached form a 5- to 8-
membered mono- or bi-cyclic ring optionally containing an additional heteroatom
selected from O, S, and NR⁷;

25 R⁹ is hydrogen or C₁₋₄ alkyl;

X is selected from the group consisting of
C₁₋₈ alkyl,
(CH₂)_nC₃₋₈cycloalkyl,
(CH₂)_naryl,
30 (CH₂)_nheteroaryl,
(CH₂)_nheterocyclyl,
(CH₂)_nC≡N,
(CH₂)_nCON(R⁸R⁸),
(CH₂)_nCO₂R⁸,

$(CH_2)_nCOR^8$
 $(CH_2)_nNR^8C(O)R^8$,
 $(CH_2)_nNR^8CO_2R^8$,
 $(CH_2)_nNR^8C(O)N(R^8)_2$,
5 $(CH_2)_nNR^8SO_2R^8$,
 $(CH_2)_nS(O)mR^8$,
 $(CH_2)_nSO_2N(R^8)(R^8)$,
 $(CH_2)_nOR^8$,
 $(CH_2)_nOC(O)R^8$,
10 $(CH_2)_nOC(O)OR^8$,
 $(CH_2)_nOC(O)N(R^8)_2$,
 $(CH_2)_nN(R^8)(R^8)$, and
 $(CH_2)_nNR^8SO_2N(R^8)(R^8)$;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups
 15 selected from R^6 , and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are unsubstituted or
 substituted with one to four groups independently selected from R^6 and oxo;

Y is selected from the group consisting of

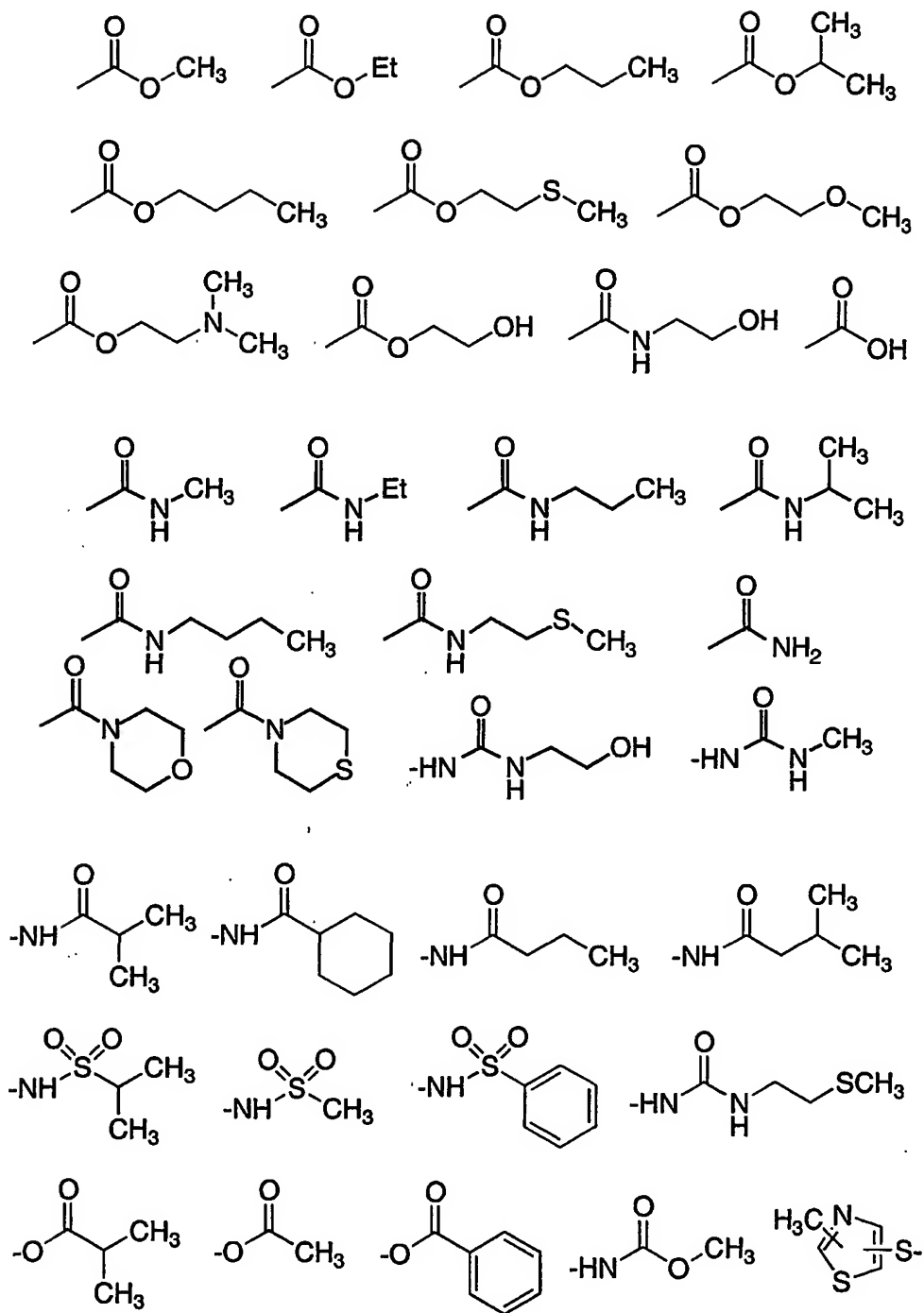
20 hydrogen,
 C₁₋₈ alkyl,
 $(CH_2)_nC_{3-6}$ cycloalkyl,
 $(CH_2)_n$ aryl, and
 $(CH_2)_n$ heteroaryl;

25 wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups
 selected from R^6 ; and alkyl, $(CH_2)_n$, and cycloalkyl are unsubstituted or substituted
 with one to three groups selected from R^6 and oxo;

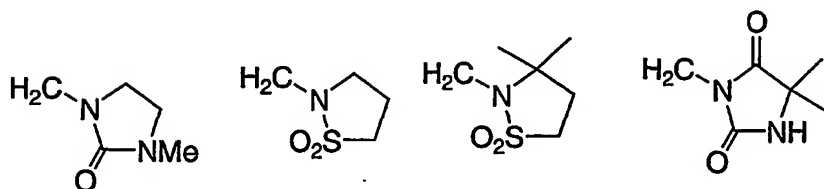
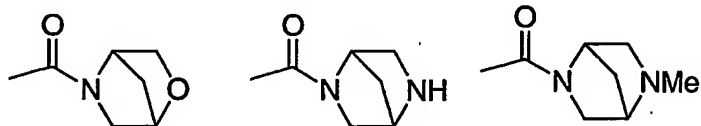
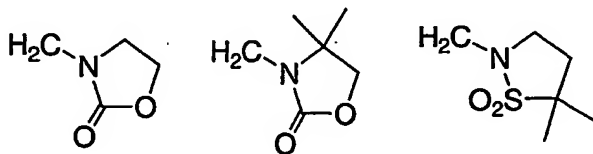
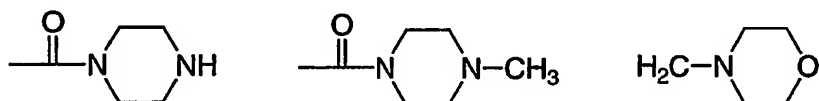
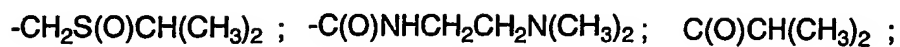
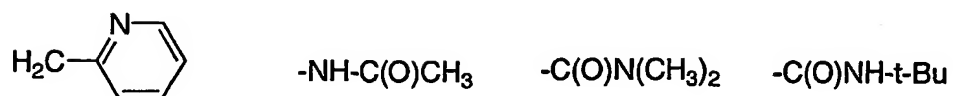
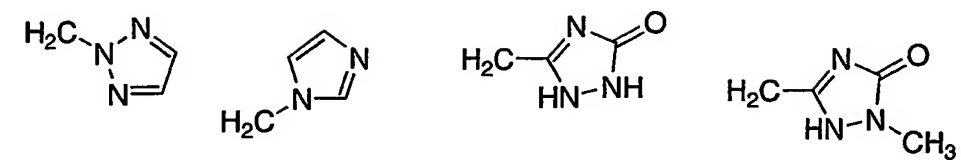
or a pharmaceutically acceptable salt thereof.

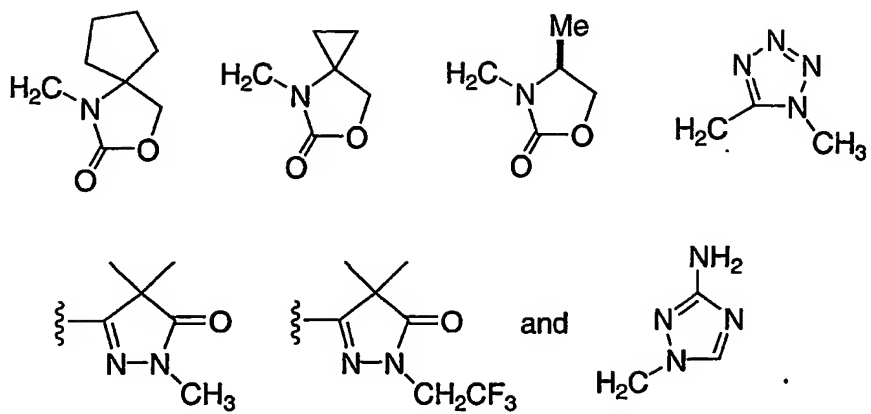
30 15. The compound of Claim 14 wherein the carbon atom marked
 with * has the *R* configuration.

16. The compound of Claim 14 wherein X is selected from the
 group consisting of:





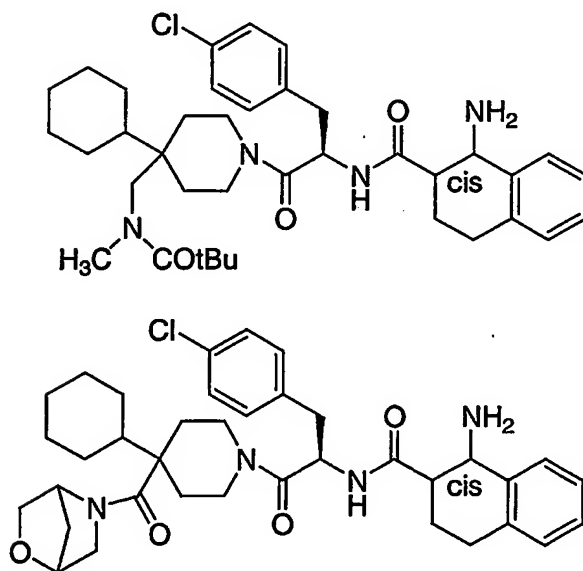


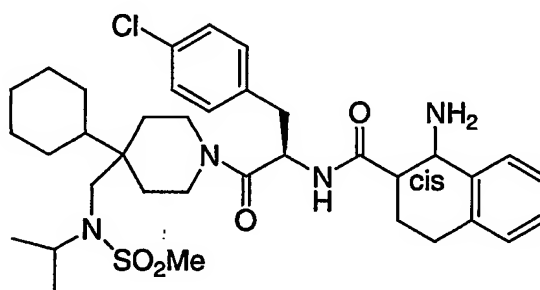
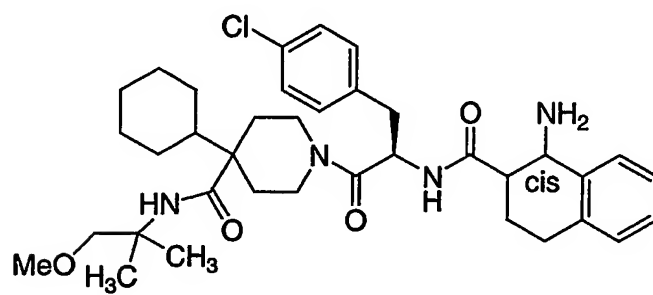
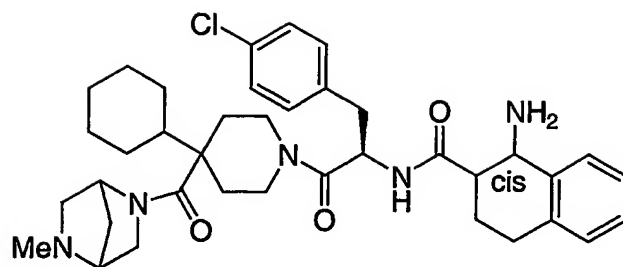


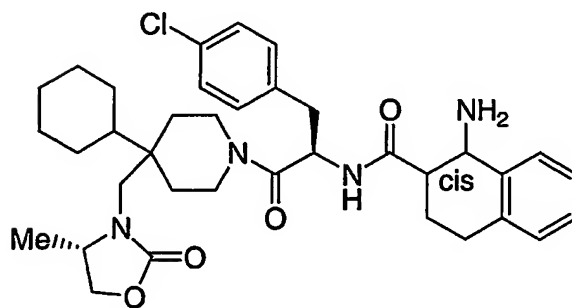
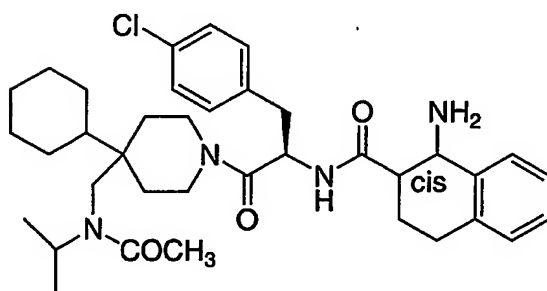
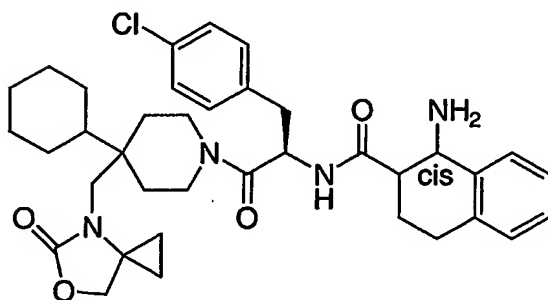
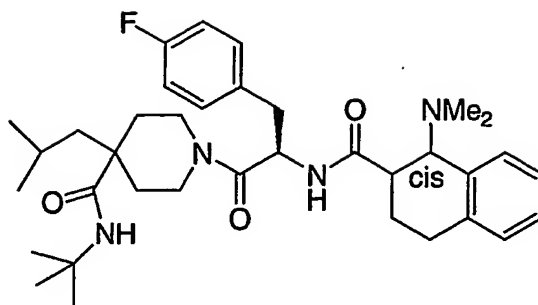
17. The compound of Claim 16 selected from the group consisting

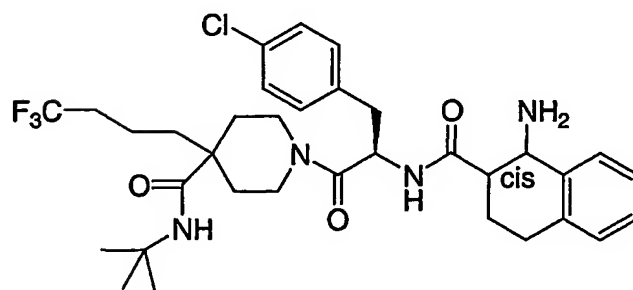
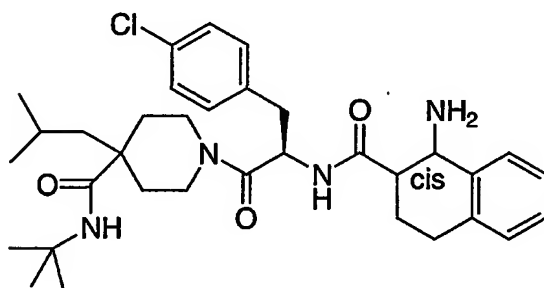
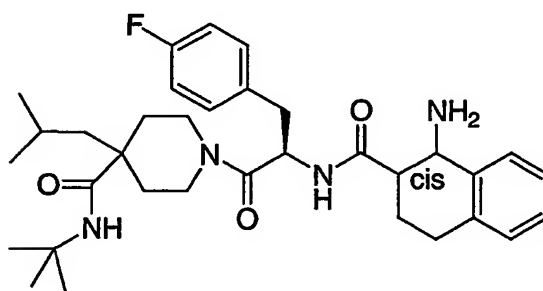
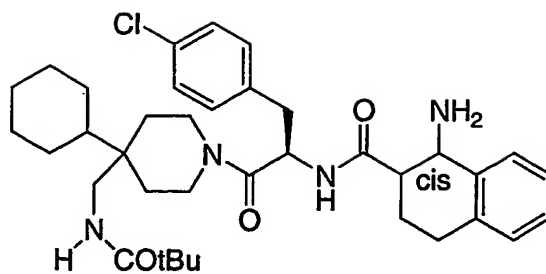
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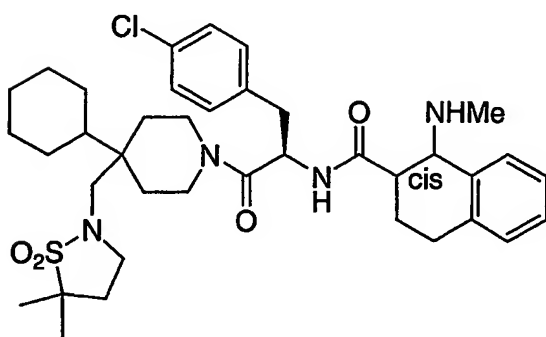
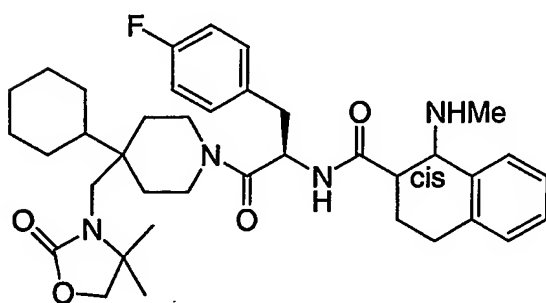
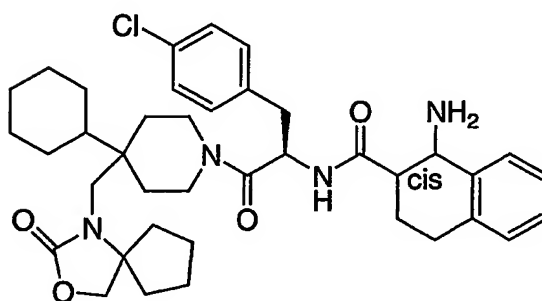
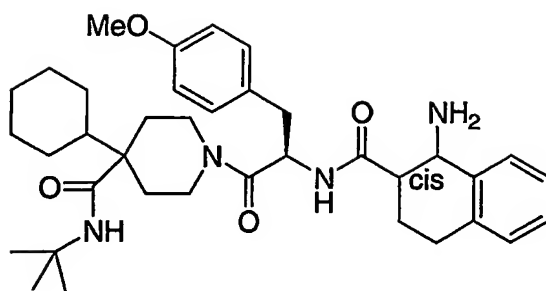
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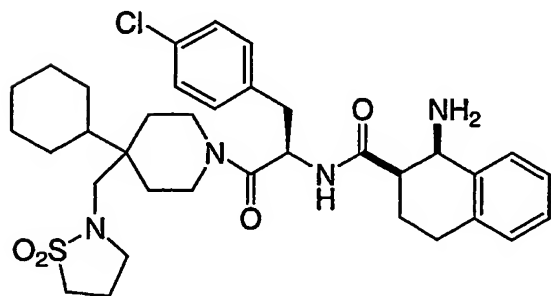
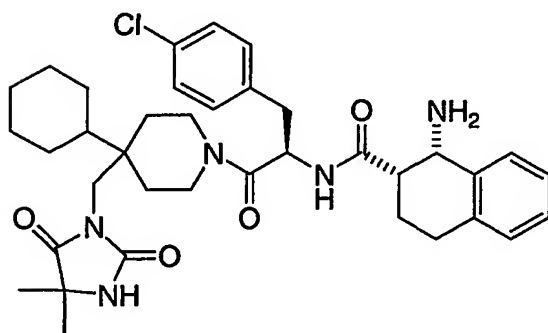
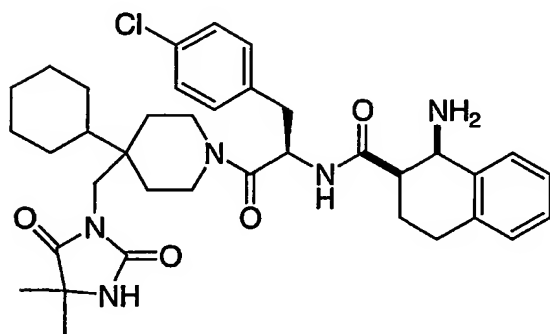
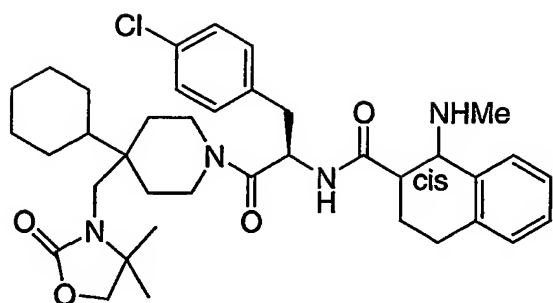


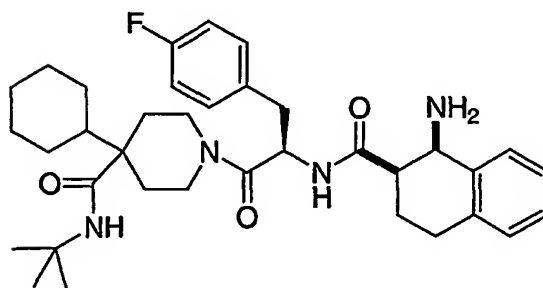
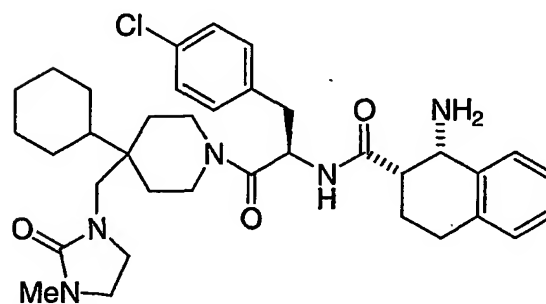
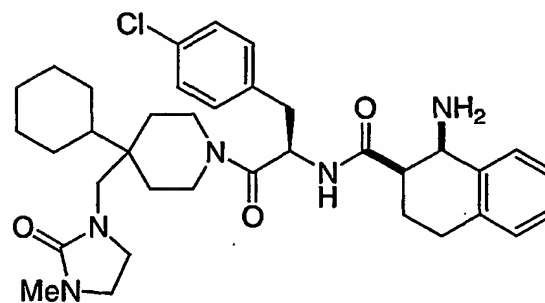
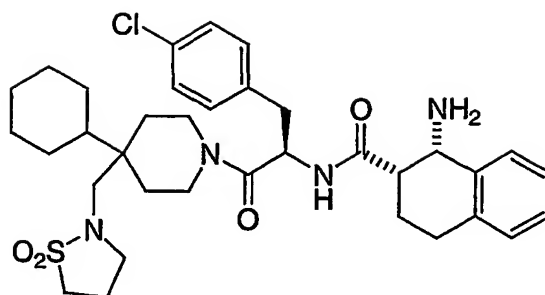


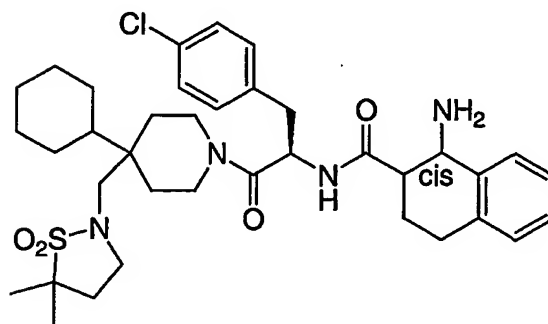
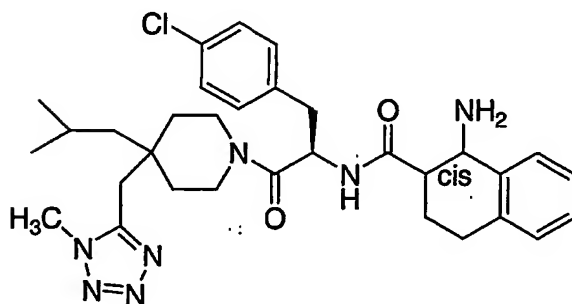
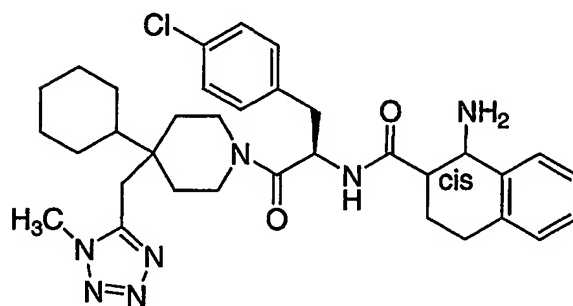
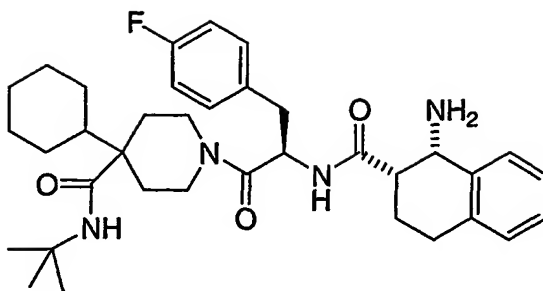


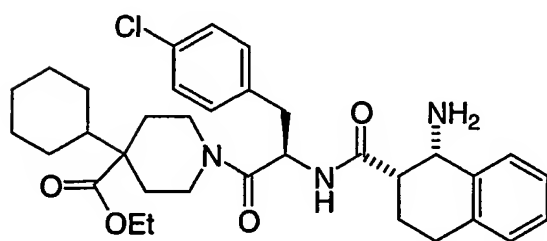
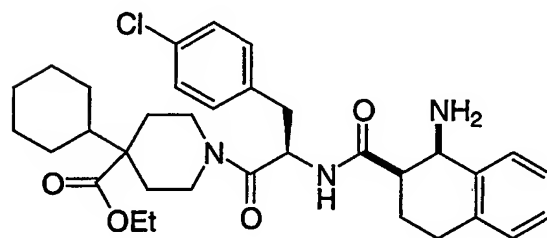
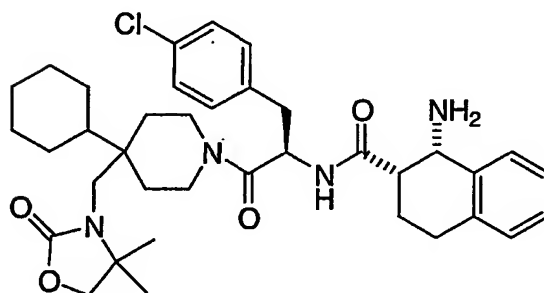
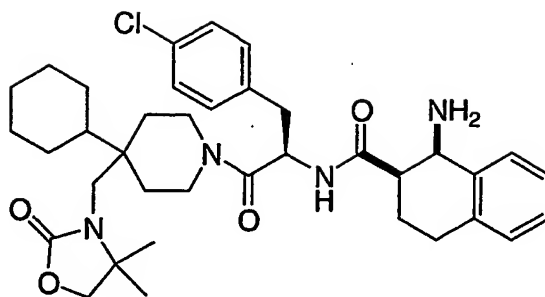


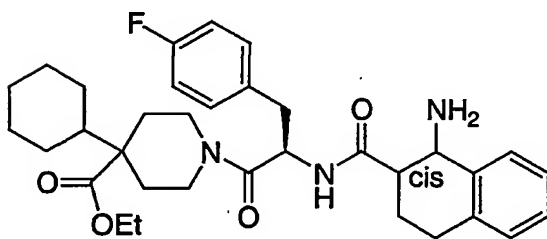
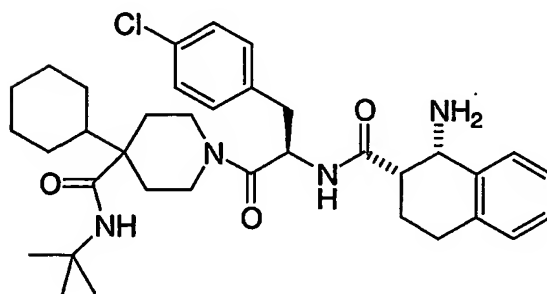
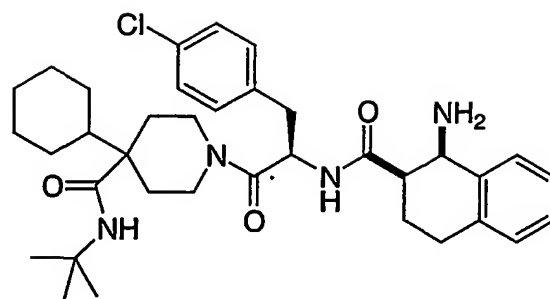


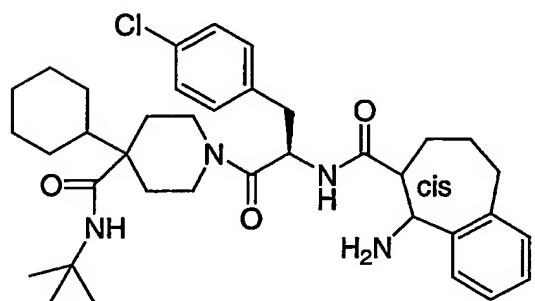
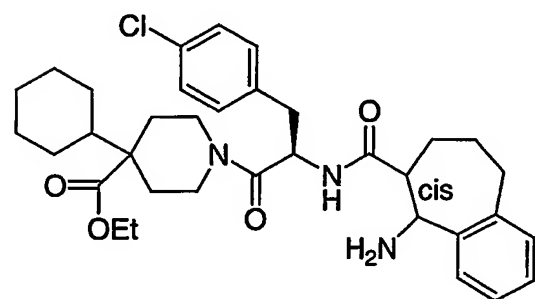
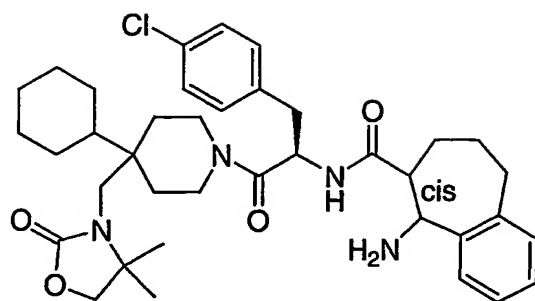


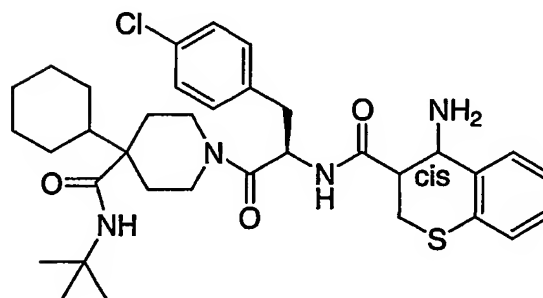
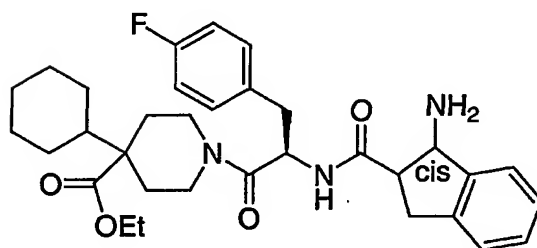
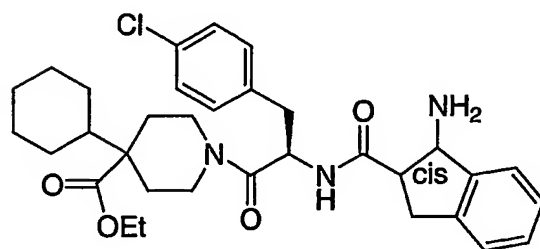
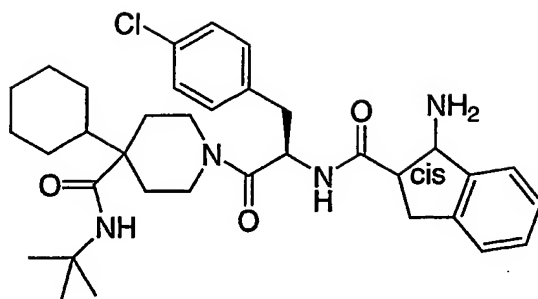


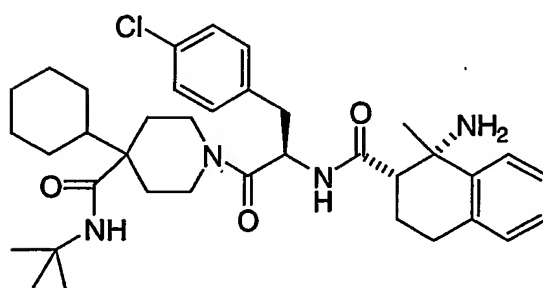
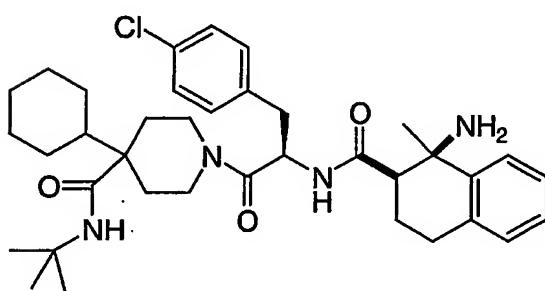
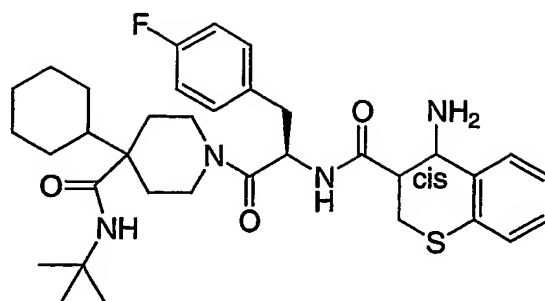


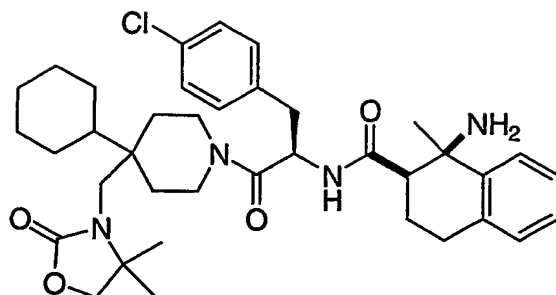




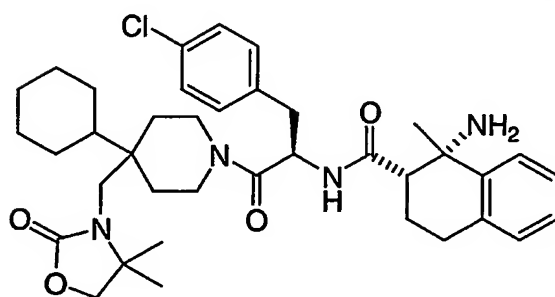








and

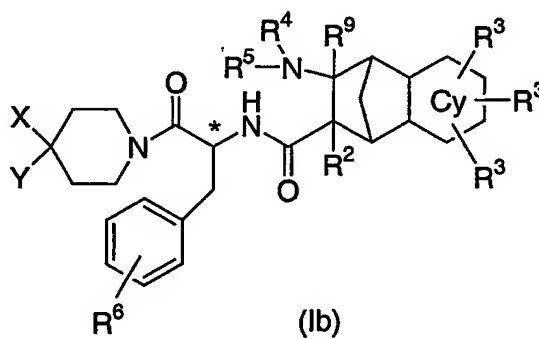


;

or a pharmaceutically acceptable salt thereof.

18. The compound of Claim 1 of formula Ib:

5



(Ib)

wherein

Cy is phenyl or cyclohexyl,

10 wherein Cy is substituted with one to three groups independently selected from R³;

n is 1 or 2;

R² is selected from the group consisting of

hydrogen,
5 C₁₋₆ alkyl, and
C₅₋₆ cycloalkyl;

each R³ is independently selected from

hydrogen,
10 C₁₋₈ alkyl,
(CH₂)_n-aryl,
(CH₂)_nC₃₋₇ cycloalkyl,
(CH₂)_n-heteroaryl,
halo,
15 OR⁷,
NHSO₂R⁷,
N(R⁷)₂,
C≡N,
CO₂R⁷,
20 C(R⁷)(R⁷)N(R⁷)₂,
NO₂,
SO₂N(R⁷)₂,
S(O)_mR⁷,
CF₃, and
25 OCF₃;

R⁴ and R⁵ are each independently selected from the group consisting of

hydrogen,
C₁₋₆ alkyl, and
30 C₅₋₆ cycloalkyl;

or R⁴ and R⁵ together with the nitrogen to which they are attached form a 5- to 8-membered ring optionally containing an additional heteroatom selected from O, S, and NR⁷;

wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups
35 independently selected from R⁶ and oxo;

- R^6 is selected from the group consisting of
- C₁₋₈ alkyl,
 - (CH₂)_n-aryl,
 - 5 (CH₂)_nC₃₋₇cycloalkyl,
 - (CH₂)_n-heteroaryl,
 - halo,
 - OR⁷,
 - NHSO₂R⁷,
 - 10 N(R⁷)₂,
 - C≡N,
 - CO₂R⁷,
 - C(R⁷)(R⁷)N(R⁷)₂,
 - NO₂,
 - 15 SO₂N(R⁷)₂,
 - S(O)_mR⁷,
 - CF₃; and
 - OCF₃;
- 20 each R⁷ is independently selected from the group consisting of
- hydrogen,
 - C₁₋₈ alkyl, and
 - C₃₋₆ cycloalkyl;
- 25 each R⁸ is independently selected from the group consisting of
- hydrogen,
 - C₁₋₅ alkyl,
 - aryl,
 - heteroaryl, and
 - 30 C₅₋₆ cycloalkyl;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R⁶; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R⁶ and oxo; or two R⁸ groups together with the atoms to which they are attached form a 5- to 8-

membered mono- or bi-cyclic ring optionally containing an additional heteroatom selected from O, S, and NR⁷;

R⁹ is hydrogen or C₁₋₄ alkyl;

- 5 X is selected from the group consisting of
 C₁₋₈ alkyl,
 (CH₂)_nC₃₋₈cycloalkyl,
 (CH₂)_naryl,
 (CH₂)_nheteroaryl,
 10 (CH₂)_nheterocyclyl,
 (CH₂)_nC≡N,
 (CH₂)_nCON(R⁸R⁸),
 (CH₂)_nCO₂R⁸,
 (CH₂)_nCOR⁸
 15 (CH₂)_nNR⁸C(O)R⁸,
 (CH₂)_nNR⁸CO₂R⁸,
 (CH₂)_nNR⁸C(O)N(R⁸)₂,
 (CH₂)_nNR⁸SO₂R⁸,
 (CH₂)_nS(O)_mR⁸,
 20 (CH₂)_nSO₂N(R⁸)(R⁸),
 (CH₂)_nOR⁸,
 (CH₂)_nOC(O)R⁸,
 (CH₂)_nOC(O)OR⁸,
 (CH₂)_nOC(O)N(R⁸)₂,
 25 (CH₂)_nN(R⁸)(R⁸), and
 (CH₂)_nNR⁸SO₂N(R⁸)(R⁸);

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R⁶; and alkyl, (CH₂)_n, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to four groups independently selected from R⁶ and oxo;

- 30 Y is selected from the group consisting of
 hydrogen,
 C₁₋₈ alkyl,
 (CH₂)_nC₃₋₆ cycloalkyl,
 35 (CH₂)_naryl, and

(CH₂)_nheteroaryl;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R⁶; and alkyl, (CH₂)_n, and cycloalkyl are unsubstituted or substituted with one to three groups selected from R⁶ and oxo;

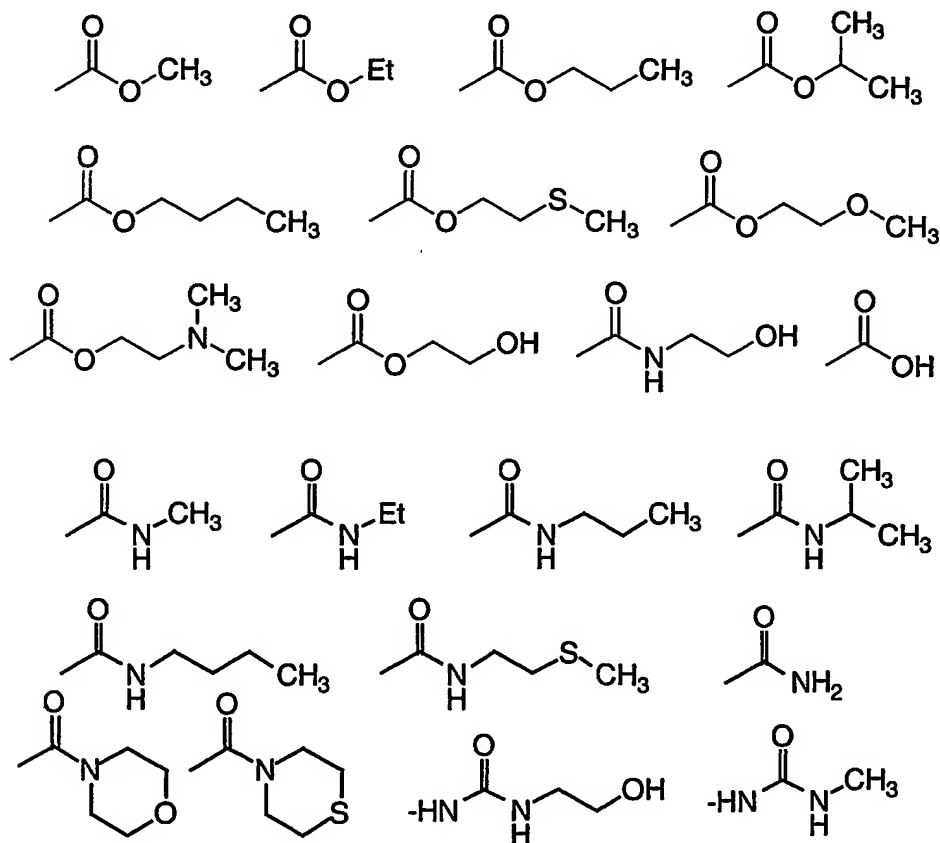
5

or a pharmaceutically acceptable salt thereof.

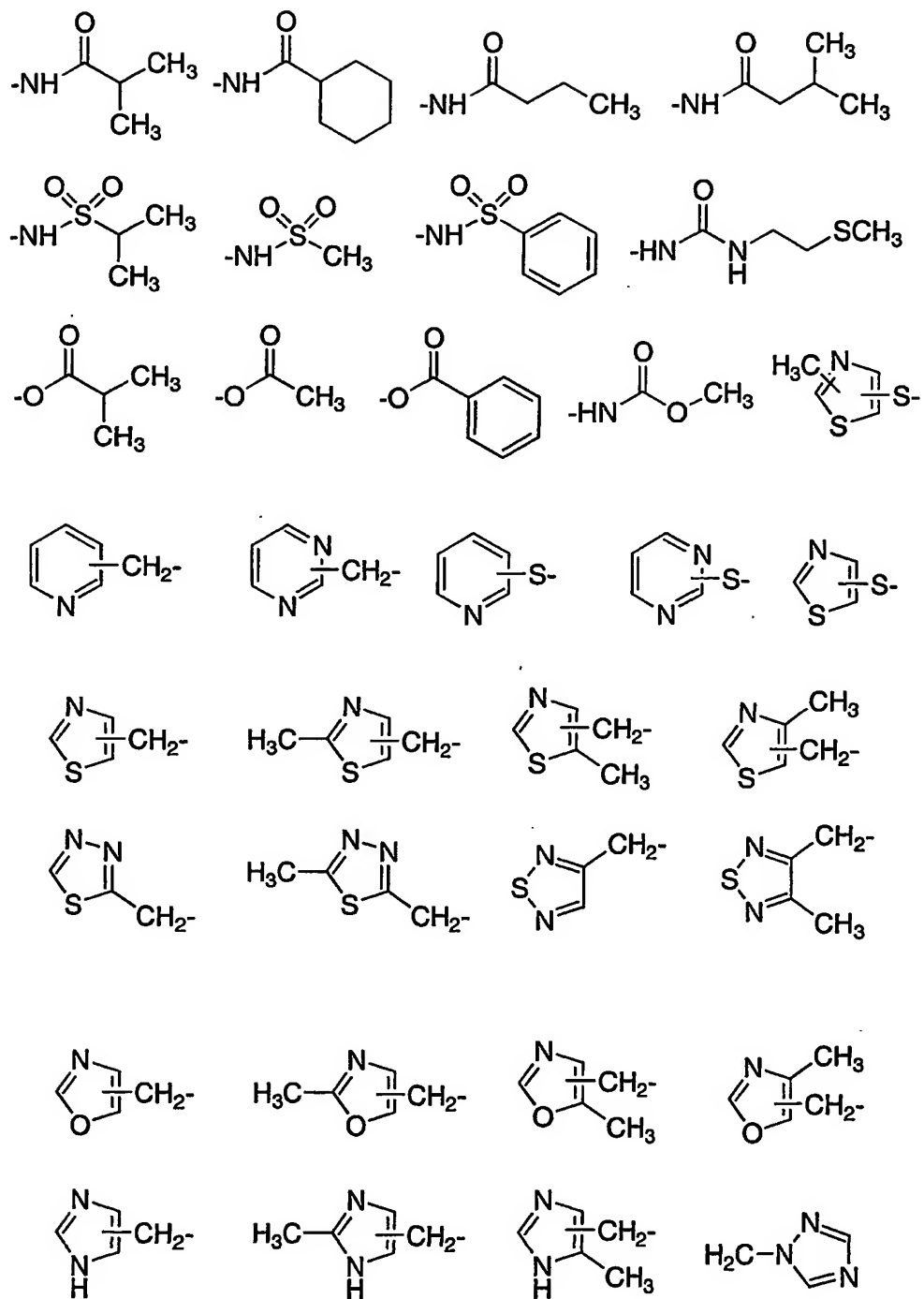
19. The compound of Claim 18 wherein the carbon atom marked with * has the *R* configuration.

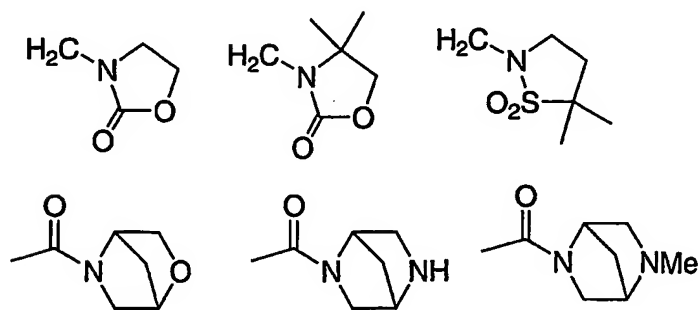
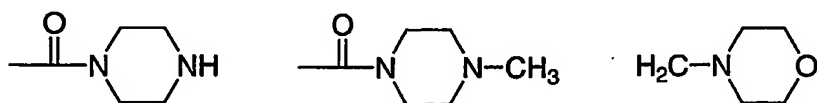
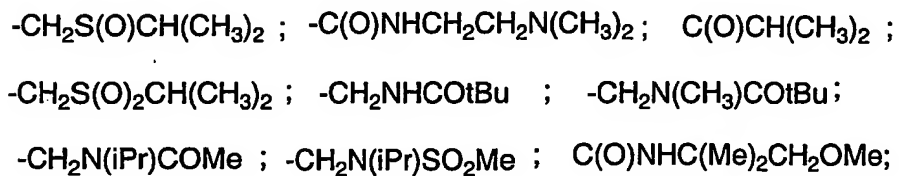
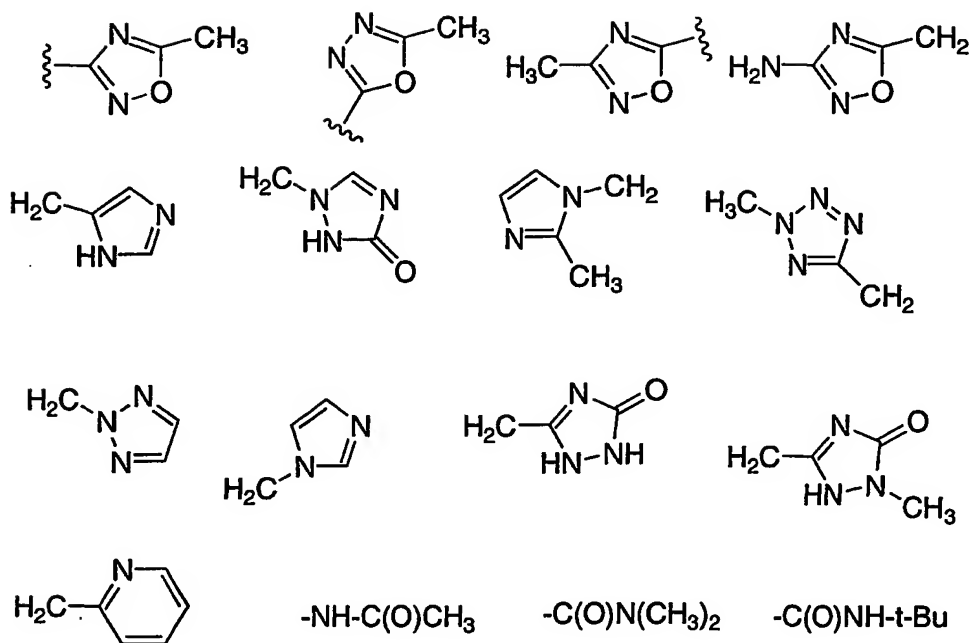
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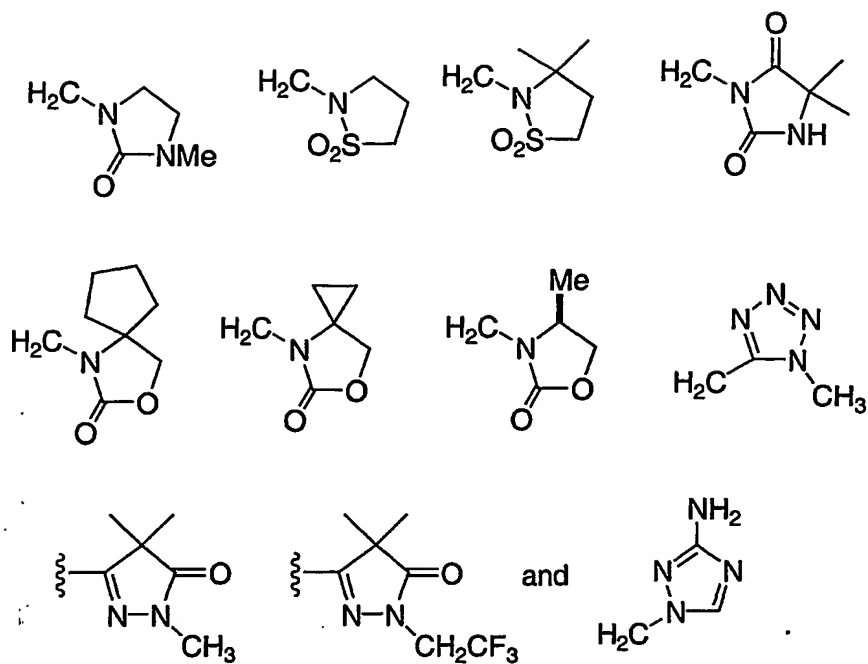
20. The compound of Claim 18 wherein X is selected from the group consisting of:



15

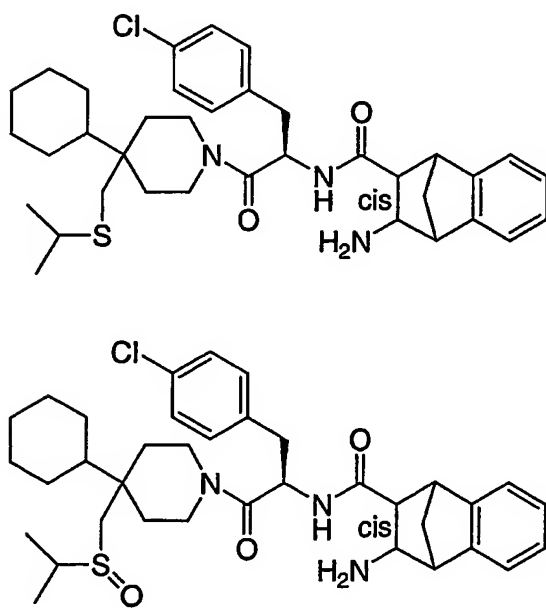


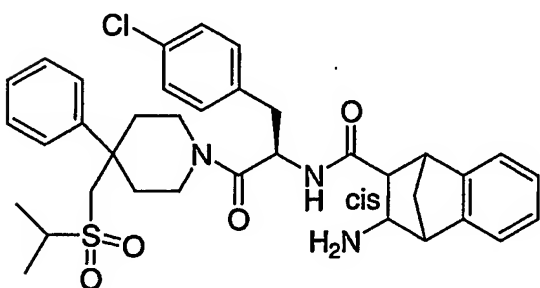
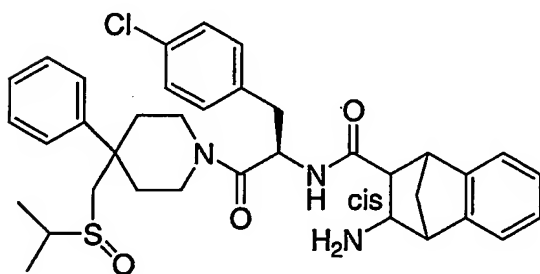
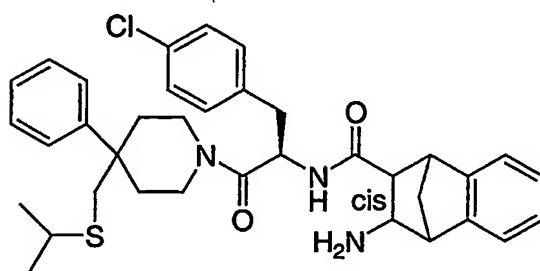
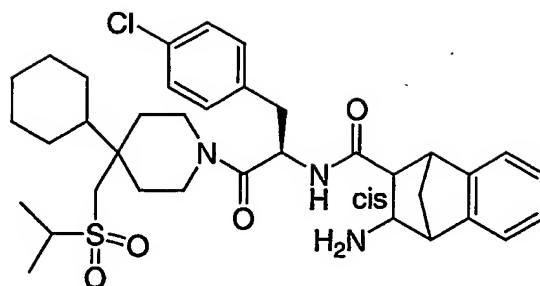


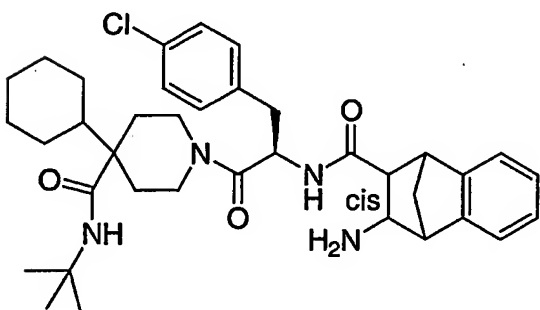
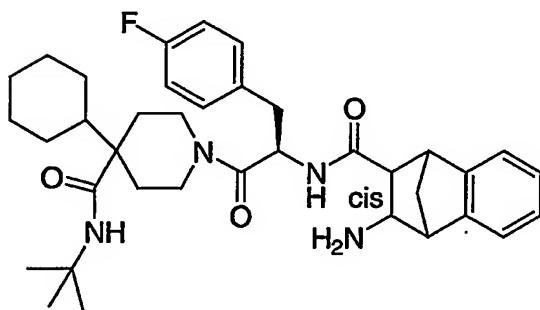
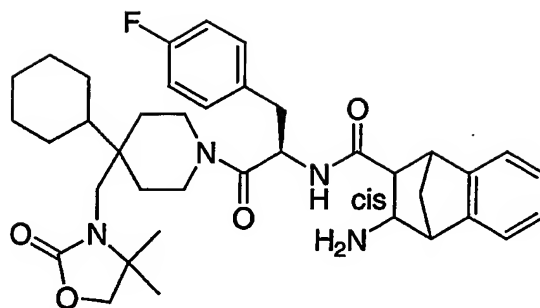


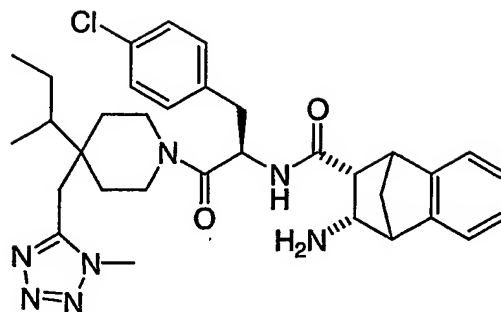
21. The compound of Claim 20 selected from the group consisting

5 of:

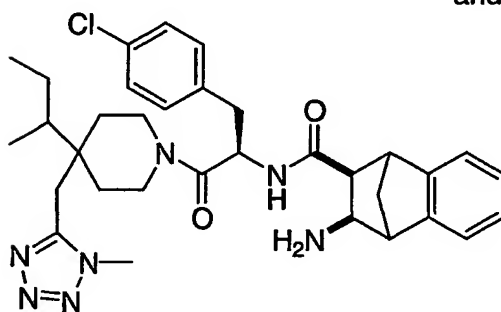








and



;

or a pharmaceutically acceptable salt thereof.

22. A method for the treatment or prevention of disorders, diseases
 5 or conditions responsive to the activation of the melanocortin receptor in a subject in
 need thereof which comprises administering to the subject a therapeutically or
 prophylactically effective amount of a compound according to Claim 1.

23. A method for the treatment or prevention of obesity in a subject
 10 in need thereof which comprises administering to the subject a therapeutically or
 prophylactically effective amount of a compound according to Claim 1.

24. A method for the treatment or prevention of diabetes mellitus
 in a subject in need thereof comprising administering to the subject a therapeutically
 15 or prophylactically effective amount of a compound according to Claim 1.

25. A method for the treatment or prevention of male or female
 sexual dysfunction in a subject in need thereof comprising administering to the

subject a therapeutically or prophylactically effective amount of a compound according to Claim 1.

26. A method for the treatment or prevention of erectile
5 dysfunction in a subject in need thereof comprising administering to the subject a therapeutically or prophylactically effective amount of a compound according to Claim 1.

27. A pharmaceutical composition which comprises a compound of
10 Claim 1 and a pharmaceutically acceptable carrier.

28. A pharmaceutical composition of Claim 27 further comprising
a second active ingredient selected from the group consisting of an insulin sensitizer,
an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, an HMG-CoA
15 reductase inhibitor, a sequestrant cholesterol lowering agent, a β 3 adrenergic receptor agonist, a neuropeptide Y antagonist, a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α 2-adrenergic receptor antagonist, and a dopaminergic agent.

29. A method of treating erectile dysfunction in a subject in need
20 thereof, comprising administering to the subject a therapeutically effective amount of the composition of Claim 28.